

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. 78N-0377 and 98P-1041; DESI 7661]

Certain Estrogen-Androgen Combination Drugs; Drugs for Human
Use; Drug Efficacy Study Implementation; Amendment and
Opportunity for Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is amending a previous FEDERAL REGISTER notice to reclassify certain estrogen-androgen combination drugs as lacking substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. The agency is taking this action because for this indication there is not substantial evidence of the contribution of each component to the effectiveness of these combination drugs. FDA is offering an opportunity for a hearing to persons affected by this action.

DATES: Requests for hearings are due on or before [insert date 30 days after date of publication in the FEDERAL REGISTER].

Data in support of hearing requests are due [insert date 60 days after date of publication in the FEDERAL REGISTER].

ADDRESSES: Communications in response to this notice should be identified with the reference number DESI 7661 and directed to

the attention of the appropriate office named below. A request for hearing, supporting data, and other comments should be identified with Docket No. 76N-0377 and submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. A request for an opinion on the applicability of this notice to a specific drug product should be directed to the Division of New Drugs and Labeling Compliance (HFD-310), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

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Center for Drug Evaluation and Research (HFD-7),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

In a notice published in the FEDERAL REGISTER of September 8, 1972 (37 FR 18225), FDA announced its evaluation of the

various indications claimed for the following combination drugs that contain an estrogen and an androgen:

1. Halodrin Tablets (NDA 11-267), containing fluoxymesterone and ethinyl estradiol;
2. Tylosterone Injection (NDA 8-099), containing diethylstilbestrol and methyltestosterone;
3. Tylosterone Tablets (NDA 7-661), containing diethylstilbestrol and methyltestosterone;
4. Tace with Androgen Capsules (NDA 10-597), containing chlorotrianisene and methyltestosterone;
5. Deladumone Injection and Deladumone OB Injection (NDA 9-545), containing testosterone enanthate and estradiol valerate.

As announced in that 1972 notice, FDA found these drugs to be safe and effective for the "prevention of postpartum breast engorgement and "for the menopausal syndrome in those patients not improved by estrogen alone."

In the FEDERAL REGISTER of December 17, 1998 (63 FR 69631), FDA withdrew approval of estrogen-containing drugs insofar as they are indicated for postpartum breast engorgement because estrogens have not been shown to be safe for this use. That FEDERAL REGISTER notice included, among others, four of the five

NDAs listed above. (NDA 11-267 was not included because the drug product covered by that application, Halodrin Tablets, was not labeled for use for postpartum breast engorgement.) Given this December 17, 1998, notice, the following discussion relates only to the second indication found safe and effective in the 1972 notice, i.e., "for the menopausal syndrome in patients not improved by estrogen alone."

In the FEDERAL REGISTER of September 29, 1976 (41 FR 43112), the agency announced that the menopausal indication for combination drugs containing an estrogen and an androgen was revised to read as follows:

Moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 41 FR 43112 at 43113. (emphasis in original)

This action was taken as one part of a large agency undertaking with respect to the labeling (patient-directed as well as physician-directed) for all estrogen-containing drug products. The following documents were also published

in the FEDERAL REGISTER of September 29, 1976: (1) 41 FR 43110 (DESI 2238; Certain Preparations for Vaginal Use); (2) 41 FR 43114 (DESI 1543; Certain Estrogen-Containing Drugs for Oral or Parenteral Use); (3) 41 FR 43117 (DESI 740, 1543, 2238, and 7661; Physician Labeling and Patient Labeling for Estrogens for General Use); and (4) 41 FR 43108 (a proposed rule that would require certain patient-directed labeling for estrogens for general use).

The five applications listed below were approved on the basis of the 1976 notice, and their approvals are withdrawn in a notice published elsewhere in today's issue of the FEDERAL REGISTER:

1. NDA 17-968 and ANDA 85-603 (testosterone cypionate 50 milligrams/milliliter (mg/mL) and estradiol cypionate 2 mg/mL injection).

2. ANDA 85-860 and ANDA 86-423 (testosterone enanthate 180 mg/mL and estradiol valerate 8 mg/mL injection).

3. ANDA 85-865 (testosterone enanthate 90 mg/mL and estradiol valerate 4 mg/mL injection).

In 1981, the Center for Drug Evaluation and Research (CDER) (then the Bureau of Drugs) determined in response to requests from the sponsors that the effectiveness finding

of the 1976 DESI 7661 FEDERAL REGISTER notice could be applied to two combination drug products that were not listed in the 1976 notice, but were being marketed at the time: (1) Conjugated estrogens and methyltestosterone and (2) esterified estrogens and methyltestosterone. Based on this finding, FDA filed (i.e., accepted for review) abbreviated new drug applications (ANDAs) for these drug products. Wyeth-Ayerst submitted ANDA 85-515 for a drug product containing 0.625 mg conjugated estrogens and 5 mg methyltestosterone, and ANDA 87-824 for a drug product containing 1.25 mg conjugated estrogens and 10 mg methyltestosterone. Reid-Provident Laboratories (subsequently acquired by Solvay Pharmaceuticals, Inc.) submitted ANDA 87-212 for a drug product containing 0.625 mg esterified estrogens and 1.25 mg methyltestosterone (Estratest H.S.), and ANDA 87-597 for a drug product containing 1.25 mg esterified estrogens and 2.5 mg methyltestosterone (Estratest).

In 1996, FDA withdrew Wyeth-Ayerst's two pending applications under 21 CFR 314.65 because the applications had been inactive for many years and Wyeth-Ayerst had stopped marketing the products. Solvay continues to market Estratest

and Estratest H.S. The ANDAs for the Estratest products have not been approved and are still pending.

FDA has withdrawn approval of all five new drug applications (NDAs) named in the 1972 and 1976 notices. The agency withdrew approval of NDA 10-597 (Tace with Androgen Capsules containing chlorotrianisene and methyltestosterone) and NDA 11-267 (Halodrin Tablets containing fluoxymesterone and ethinyl estradiol) in FEDERAL REGISTER notices of June 25, 1993 (58 FR 34466), and March 2, 1994 (59 FR 9989), respectively. The agency withdrew approval of NDA 7-661 (Tylosterone Tablets) and NDA 8-099 (Tylosterone Injection), both containing diethylstilbestrol and methyltestosterone, and NDA 9-545 (Deladumone OB Injection and Deladumone Injection, each containing testosterone enanthate and estradiol valerate) in a notice published in the FEDERAL REGISTER of October 29, 1998 (63 FR 58053).

In response to the notice of October 29, 1998, on November 24, 1998, Solvay Pharmaceuticals submitted a citizen petition (Docket No. 98P-1041) requesting that FDA determine that the products covered by the three applications withdrawn in the October 21, 1998, notice were not withdrawn for reasons of safety or effectiveness. As FDA is doing for the five estrogen-

androgen combination products whose approvals are being withdrawn in a notice published elsewhere in today's issue of the FEDERAL REGISTER, the agency is deferring to the outcome of this proceeding to amend the 1976 notice the determination of whether the products covered by the three applications named in Solvay's petition were withdrawn for reasons of safety or effectiveness. If the proceeding to amend the 1976 notice determines that there is substantial evidence of effectiveness of the estrogen-androgen combination products for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone, then the products covered by the three applications named in Solvay's petition, as well as the five products referred to in a notice published elsewhere in today's issue of the FEDERAL REGISTER, will be regarded as not withdrawn for reasons of effectiveness.

As mentioned previously, there are two pending ANDAs for Solvay's Estratest and Estratest H.S., originally filed in 1981. However, as described in detail below, FDA no longer believes that estrogen-androgen combination drug products are effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. FDA, therefore, has initiated this proceeding

to amend the DESI finding of effectiveness for these products. This proceeding is limited to a determination of whether there is substantial evidence of the effectiveness of estrogen-androgen combination drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. The use of these combination drug products for any other use, including but not limited to the treatment of other menopausal symptoms, will not be considered in this proceeding. The effectiveness of estrogen-androgen combination products for indications not covered by this proceeding should be addressed through the new drug application process.

II. The Safety and Effectiveness of Estrogen-Androgen Combination Drug Products for the Treatment of Vasomotor Symptoms Associated with Menopause in Patients Not Improved by Estrogen Alone

The agency took a renewed interest in estrogen-androgen combination drug products when concerns were raised about the effect of androgens in lowering high-density lipoproteins (Refs. 1 and 2). It is believed that oral androgens can reverse the favorable impact of estrogen on lipoproteins (Ref. 3). Other

safety concerns were virilization (Refs. 4 and 5) and possible liver toxicity (Refs. 6, 7, and 8).

FDA concluded that the negative effects androgens may have on lipid profile may be offset by a potential positive effect on bone mineral density (Refs. 1, 9, and 10).

With respect to virilization (i.e., hirsutism, acne, deepening of the voice, alopecia, and clitoromegaly), FDA observed that the incidence varied widely in clinical studies and appeared to be dose and duration dependent. In a 2-year trial of 33 women treated with methyltestosterone 2.5 mg and esterified estrogen 1.25 mg daily, 36 percent reported a hair disorder and 30 percent reported acne (Ref. 1). In the same 2-year trial of 33 women treated with esterified estrogen 1.25 mg daily, 3 percent reported a hair disorder and 6 percent reported acne (Ref. 1). In another trial at 24 months, 10 of the 154 women treated with methyltestosterone and esterified estrogens and 3 of the 157 women treated with esterified estrogens reported hirsutism (Ref. 9).

FDA does not believe there is a serious risk for possible liver toxicity at the relatively low doses of androgen administered in standard oral estrogen-androgen combination therapies (Refs. 11, 12, and 13).

An agency review of the literature regarding safety concerns led to scrutiny of the labeled indication, that is, moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.

Estrogen-alone drug products are approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Vasomotor symptoms associated with the menopause are, simply put, "hot flushes." A hot flush is a sudden feeling of heat, usually on the face, neck, shoulders, and chest. Hot flushes have been described as "recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitation, feeling of anxiety, and sometimes followed by chills" (Ref. 14). When hot flushes occur at night, they are often called night sweats.

The indication for estrogen-androgen combination drug products is limited to that subset of women with "moderate to severe vasomotor symptoms associated with the menopause" that are "not improved by estrogen alone" (emphasis added). The precise wording of the indication quite narrowly defines the intended population. Thus, to be found effective for this narrow indication, there would need to be reliable evidence that estrogen-androgen combination products are effective in treating

the population of menopausal women whose vasomotor symptoms are not relieved by estrogen alone.

FDA believes that substantial evidence is lacking that the addition of an androgen can improve the effectiveness of estrogen alone in the treatment of vasomotor symptoms (i.e., hot flushes). An early randomized, placebo-controlled, five-arm, two-period crossover clinical trial by Sherwin and Gelfand (Ref. 15) compared the effects on surgically menopausal women of immediate postoperative parenteral administration of estrogen alone (n=11), androgen alone (n=10), estrogen and androgen in combination (n=12), and placebo (n=10) to hysterectomy controls (n=10) and found that the androgen alone, estrogen-androgen combination, and control hysterectomy groups had lower (i.e., lower frequency and severity) menopausal somatic symptoms scores than the estrogen alone and placebo groups. The menopausal somatic symptoms score evaluated a constellation of symptoms including hot flushes, cold sweats, weight gain, rheumatic pains, cold hands and feet, breast pains, headaches, numbness and tingling, and skin crawls. A single-center, double-blind randomized, 6-month study by Hickok, Toomey, and Speroff (Ref. 2) compared the effects of treating surgically menopausal women with esterified estrogens alone (n=13) or in combination with

methyltestosterone (n=13) on a similar constellation of menopausal symptoms, but found no statistically significant difference between the two treatments. The 15 menopausal symptoms evaluated were hot flushes, cold sweats, vaginal dryness, cold hands and feet, breast pain or tenderness, numbness and tingling, skin crawls, edema, increased facial or body hair, voice deepening, acne, trouble sleeping, pounding of the heart, dizzy spells, and pressure or tightness in the head or body. A 2-year, multicenter, double-blind, randomized, parallel group study (Ref. 9) comparing the effects of 2 doses of conjugated equine estrogen and 2 doses of esterified estrogen plus methyltestosterone in a total of 311 surgically menopausal women found no differences among the groups in relief of hot flashes, sweats, and vaginal dryness.

Clinical studies that evaluated the effect of estrogen-androgen combination therapy specifically on hot flushes found that the combination does not reduce the frequency of vasomotor symptoms more than estrogen alone. Watts et al. (Ref. 1) compared treatment with esterified estrogens alone and treatment with esterified estrogens and methyltestosterone in a 2-year, multicenter, double-blind, randomized, parallel group study conducted in 66 surgically menopausal women. The authors found

no significant difference in the mean reduction from baseline in the number of hot flushes between the two groups. Sarrel et al. (Ref. 17) found no meaningful differences in relief from hot flushes when 20 postmenopausal women were treated for 8 weeks with esterified estrogens or an esterified estrogens-androgen combination in a single-center, double-blind, randomized, parallel group study. Burger (Ref. 18) administered subcutaneous implants of estradiol and testosterone to 17 menopausal women who complained that symptoms persisted, particularly loss of libido, despite treatment with conjugated equine estrogens. There was no statistically significant change from baseline in hot flushes after treatment. Myers et al. (Ref. 19) conducted a 10-week, double-blind, placebo controlled, parallel group study in 40 naturally menopausal women comparing 4 treatments: Conjugated estrogens alone, conjugated estrogens and medroxyprogesterone, conjugated estrogens and androgen, and placebo. The study found that the estrogen and estrogen/medroxyprogesterone groups had significantly fewer hot flashes than the estrogen/androgen or placebo groups. The authors concluded: "This result is consistent with other studies showing no effect of androgen alone on hot flashes" (Ref. 19, p. 1129).

Other authors affirm the conclusion that estrogen-androgen combination drug products are not superior to estrogen in reducing vasomotor symptoms (Refs. 3, 20 through 23). Rosenberg summarized the evidence concerning the alleviation of vasomotor symptoms as follows: "Studies suggest that estrogen is primarily responsible for reductions in vasomotor symptoms and that the addition of androgen neither improves nor detracts from this beneficial effect" (Ref. 24, p. 400).

III. FDA's Conclusions Concerning the Safety and Effectiveness of Estrogen-Androgen Combination Drug Products

For the reasons discussed previously, FDA no longer regards combination drug products containing estrogen(s) and androgen(s) as having been shown to be effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. The agency has closely examined the data and information that formed the basis for the 1976 finding that such combinations were effective for this indication, as well as the subsequent literature, and has determined that there is a lack of substantial evidence that this combination is effective for "moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone."

IV. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Watts, N. B. et al., "Comparison of Oral Estrogens and Estrogens Plus Androgen on Bone Mineral Density, Menopausal Symptoms, and Lipid-Lipoprotein Profiles in Surgical Menopause," Obstetrics & Gynecology, 85:529-537, 1995.

2. Hickok, L. R., C. Toomey, and L. Speroff, "A Comparison of Esterified Estrogens With and Without Methyltestosterone: Effects on Endometrial Histology and Serum Lipoproteins in Postmenopausal Women," Obstetrics & Gynecology, 82:919-924, 1993.

3. Kaunitz, A. M., "The Role of Androgens in Menopausal Hormonal Replacement," Endocrinology and Metabolism Clinics of North America, 26(2):391-397, 1997.

4. ACOG Committee on Gynecologic Practice, "Committee Opinion: Androgen Treatment of Decreased

Libido," 2002 Compendium of Selected Publications, American College of Obstetricians and Gynecologists, Washington, DC, pp. 5-6, 2002.

5. Gelfand, M. M., and B. Wiita, "Androgen and Estrogen-Androgen Hormone Replacement Therapy: A Review of the Safety Literature, 1941 to 1996," Clinical Therapeutics, 19(3):383-399, 1997.

6. Westaby, D. et al, "Liver Damage from Long-Term Methyltestosterone," Lancet, 2:262-263, 1977.

7. Turani, H. et al., "Hepatic Lesions in Patients on Anabolic Androgenic Therapy," Israel Journal of Medical Sciences, 19:332-337, 1983.

8. Lucey, M. R., and R. H. Moseley, "Severe Cholestasis Associated With Methyltestosterone: A Case Report," American Journal of Gastroenterology, 82:461-462, 1987.

9. Barrett-Connor, E. et al, "A Two-Year, Double-Blind Comparison of Estrogen-Androgen and Conjugated Estrogens in Surgically Menopausal Women," Journal of Reproductive Medicine, 44:1012-1020, 1999.

10. Raisz, L. G. et al, "Comparison of the Effects of Estrogen Alone and Estrogen Plus Androgen

on Biochemical Markers of Bone Formation and Resorption in Postmenopausal Women," Journal of Clinical Endocrinology and Metabolism, 81:37-43, 1996.

11. Gitlin, N., P. Korner, and H. Yang, "Liver Function in Postmenopausal Women on Estrogen-Androgen Hormone Replacement Therapy: A Meta-Analysis of Eight Clinical Trials," Menopause, 6(3):216-224, 1999.

12. Ettinger, B., "Letter: Estrogen-Androgen Hepatotoxicity," American Journal of Obstetrics and Gynecology, 178(3):627-628, 1998.

13. Phillips, E., and C. Bauman, "Safety Surveillance of Esterified Estrogens-Methyltestosterone (ESTRATEST and ESTRATEST HS) Replacement Therapy in the United States," Clinical Therapeutics, 19(5):1070-1084, 1997.

14. Kronenberg, F., "Hot Flashes: Epidemiology and Physiology," Annals of the New York Academy of Sciences, 592:52-86, 1990.

15. Sherwin, B., and M. Gelfand, "Differential Symptom Response to Parenteral Estrogen and/or Androgen Administration in the Surgical Menopause,"

American Journal of Obstetrics and Gynecology,
151(2):153-160, 1985.

16. Barrett-Connor, E., "Efficacy and Safety of Estrogen/Androgen Therapy," Journal of Reproductive Medicine, 43(8-Suppl.):746-752, 1998.

17. Sarrel, P. et al., "Estrogen and Estrogen-Androgen Replacement in Postmenopausal Women Dissatisfied with Estrogen-Only Therapy," Journal of Reproductive Medicine, 43(10):847-856, 1998.

18. Burger, H. et al., "The Management of Persistent Menopausal Symptoms with Oestradiol-Testosterone Implants: Clinical, Lipid and Hormonal Results," Maturitas, 6:351-358, 1984.

19. Myers, L. S. et al., "Effects of Estrogen, Androgen and Progestin on Sexual Psychophysiology and Behavior in Postmenopausal Women," Journal of Clinical Endocrinology and Metabolism, 70(4):1124-1131, 1990.

20. Greenblatt, R. B. et al., "Evaluation of an Estrogen, Androgen, Estrogen-Androgen Combination, and a Placebo in the Treatment of the Menopause," Journal of Clinical Endocrinology and Metabolism, 10:1547-1558, 1950.

21. McNagny, S. E., "Prescribing Hormone Replacement Therapy for Menopausal Symptoms," Annals of Internal Medicine, 131(8):605-616, 1999.

22. Barlow, D. H. et al., "Long-Term Hormone Implant Therapy--Hormonal and Clinical Effects," Obstetrics & Gynecology, 67:321-325, 1986.

23. Rymer, J., and E. Morris, "Menopausal Symptoms," Clinical Evidence, 5: 1308-1310, June 2001.

24. Rosenberg, M. J., T. D. N. King, and M. C. Timmons, "Estrogen-Androgen for Hormone Replacement: A Review," Journal of Reproductive Medicine, 42(7):394-404, 1997.

V. Amendment

Based on the findings discussed in section II of this document, FDA is amending the FEDERAL REGISTER notice of September 29, 1976 (41 FR 43112), to reclassify estrogen-androgen combination drugs as lacking substantial evidence of effectiveness for moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.

Drug products covered by this notice (i.e., estrogen-androgen combination drugs) are regarded as new drugs (section

201(p) of the Federal Food, Drug, and Cosmetic Act (the act) 21 U.S.C. 321(p)). An approved NDA is required for marketing.

VI. Notice of Opportunity for a Hearing

Any manufacturer or distributor of a drug product affected by this notice is hereby offered an opportunity for a hearing to show why estrogen-androgen combination drugs should not be reclassified as lacking substantial evidence of effectiveness for moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone.

This notice applies to the particular estrogen-androgen combination drugs named in this notice and to any identical, related, or similar drug product under § 310.6 (21 CFR 310.6), whether or not it is the subject of an approved NDA or ANDA. Estrogen-androgen combination drugs subject to this notice include, but are not limited to, the following combination drugs: fluoxymesterone and ethinyl estradiol; diethylstilbestrol and methyltestosterone; chlorotrianisene and methyltestosterone; testosterone enanthate and estradiol valerate; testosterone cypionate and estradiol cypionate; and esterified estrogens and methyltestosterone.

It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers

any drug product that the person manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of New Drugs and Labeling Compliance (see ADDRESSES).

A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing, together with a well-organized and full factual analysis of the clinical and other investigational data that the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations as described in 21 CFR 314.126.

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in § 310.6), e.g., any contention that any such drug product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act under the exemption for drug products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any

other reason. With respect to the issue of effectiveness, however, this notice is limited to whether there is substantial evidence of the effectiveness of estrogen-androgen combination drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. The use of these drug products for any indication other than for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone will not be considered in this proceeding.

Any person subject to this notice who decides to seek a hearing shall file: (1) On or before [insert date 30 days after date of publication in the FEDERAL REGISTER], a written notice of appearance and request for hearing, and (2) on or before [insert date 60 days after date of publication in the FEDERAL REGISTER], the data, information, and analyses relied on to demonstrate that there is a genuine issue of material fact to justify a hearing. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a

hearing are contained in § 314.200 (21 CFR 314.200) and in 21 CFR part 12.

The failure of any person subject to this notice to file a timely written notice of appearance and request for hearing, as required by § 314.200, constitutes an election by that person not to use the opportunity for a hearing concerning the action proposed and a waiver of any contentions concerning the legal status of that person's drug product(s). Any new drug product marketed without an approved new drug application is subject to regulatory action at any time, but any person subject to this notice who files a timely written notice of appearance and request for hearing and who remains a party to this proceeding will not be subject to regulatory action for matters covered by this notice until the conclusion of this proceeding. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact to justify a hearing, or if a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 21 U.S.C. 352, 355) and under authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.100).

Dated: April 4, 2003.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc 03-????? Filed ??-??-03; 8:45 am]

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